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The Neuroimaging Findings in Sotos Syndrome

G. Bradley Schaefer,[1*] John B. Bodensteiner,[2] Bruce A. Buehler,[1] Angela Lin,[3] and Trevor R.P. Cole[4]

[1]*Meyer Rehabilitation Institute, Department of Pediatrics, University of Nebraska, Omaha*
[2]*Departments of Neurology and Pediatrics, West Virginia University, Morgantown*
[3]*Boston, Massachusetts*
[4]*Clinical Genetics Unit, Birmingham Maternity Hospital, Birmingham, United Kingdom*

We reviewed the neuroimaging studies of 40 patients with classic Sotos syndrome. The studies consisted of CT scans only in 4 patients and one or more MRI scans in 36 patients. The diagnosis of Sotos syndrome was made using well-established clinical criteria. The neuroimaging studies of each patient were evaluated subjectively by visual inspection and the chief findings were tabulated and grouped into five categories: 1) ventricular abnormalities, 2) extracerebral fluid spaces, 3) midline abnormalities, 4) migrational abnormalities, and 5) others. The most common abnormality of the cerebral ventricles was prominence of the trigone (90%), followed by prominence of the occipital horns (75%) and ventriculomegaly (63%). The supratentorial extracerebral fluid spaces were increased for age in 70% of the patients and the fluid spaces in the posterior fossa were increased in 70% also. A variety of midline abnormalities were noted but anomalies of the corpus callosum were almost universal. Gray matter heterotopias occurred in only 3 (8%) of 36 patients. Periventricular leukomalacia, presumably the result of prenatal or perinatal difficulties and unrelated to the basic condition, was the most common of the miscellaneous other abnormalities noted. The neuroimaging findings of Sotos syndrome are distinct enough to allow differentiation of this syndrome from other mental retardation syndromes with macrocephaly. Am. J. Med. Genet. 68:462–465, 1997.

KEY WORDS: cerebral gigantism; overgrowth syndromes; ventriculomegaly; hypoplastic corpus callosum; cavum septum pellucidum; macrocephaly

INTRODUCTION

Sotos syndrome has been recognized for over 30 years since the description of five children with macrocephaly, somatic overgrowth, characteristic facial appearance, and mental retardation by Sotos et al. [1964]. The diagnostic signs of the syndrome include prenatal overgrowth, advanced bone age, and developmental delay most prominent early in life with frequent amelioration of the delays with age [Cole and Hughes, 1994; Wit et al., 1985]. Neuroimaging abnormalities have been tabulated in small groups of these patients [Wit et al., 1985] and we have reported quantitative analysis of selected brain structures [Schaefer and Buehler, 1992] and cerebellar vermis [Schaefer et al., 1996] in a subset of these patients. However, there are no studies which delineate the findings of visual inspection of the neuroimaging studies in a large group of patients with Sotos syndrome. We report here a study of the neuroimaging findings, as determined by visual inspection, of 40 patients with classic Sotos syndrome.

PATIENTS AND METHODS

The neuroimaging studies of patients were obtained with the aid of the Sotos Syndrome Support Association. All patients were seen by at least two clinical geneticists involved in this study (G.B.S., B.A.B., A.L., T.R.P.C.). Only those patients with unambiguous "classic" Sotos syndrome [Cole and Hughes, 1994] were included in this study. At least one Magnetic Resonance Imaging (MRI) scan was available for study on 36 patients and computed tomographic (CT) scans only were available on 4 patients. Each of the scans was visually inspected by two of the authors (J.B.B. and G.B.S.) and the identified anomalies were tabulated. Quantitative morphometric analysis was not performed on these scans as the purpose of the study was to establish the nature and frequency of the neuroimaging findings that might be appreciated by visual inspection alone. The observations were grouped into five categories: 1) ventricular abnormalities, 2) extracerebral CSF spaces, 3) midline variations, 4) migrational abnormalities, and 5) others.

RESULTS

Abnormalities of the ventricular system and the corpus callosum are present in more than 3/4 of the patients. The lateral ventricles, which were often large

*Correspondence to: Dr. G. Bradley Schaefer, University of Nebraska Medical Center, 600 South 42nd Street, P.O. Box 985430, Omaha, NE 68198-5430.

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(63%), were characterized by prominence of the trigone and the occipital horns (90% and 75% respectively) (Table I). There were no patients without at least one of these ventricular abnormalities.

The size and configuration of the corpus callosum could not be determined in the patients with CT scans only; however, one of the patients with a CT only had agenesis of the corpus callosum leaving only three patients in whom the corpus callosum could not be evaluated properly. Of the patients with MRI scans, 35 of 36 had subjective thinning of the callosum. The most characteristic configuration of the corpus callosum is thinning of the posterior third of the body (64%) with preservation of the rostrum, genu and splenium (Fig. 1).

Subjectively increased supratentorial or posterior fossa spaces occurred in 34 of 40 patients. Twenty-eight (70%) of the group had increased supratentorial CSF spaces and twenty-eight (70%) had increased CSF spaces in the posterior fossa.

One patient had complete agenesis of the corpus callosum. Abnormalities of midline structures in addition to the corpus callosum included cavum septum pellucidum (16/40, 40%), cavum vergae (15/40, 38%), cavum velum interpositum (7/40, 18%), and macrocisterna magna (3/36, 17%). The cerebellar vermis was considered to demonstrate a prominent folia pattern on occasion.

Periventricular leukomalacia characterized by abnormal signal intensity of the parietal-occipital white matter on T_2 weighted images was seen in 5 of 36 patients with MRI scans. Review of the medical histories for these patients revealed significant perinatal events that could account for these changes in four of the five patients. Recognizable gray matter heterotopias near the posterior lateral wall of the lateral ventricles were seen in three patients. Two patients were thought to have a larger than normal cerebellum and one had an open operculum defined by separation of the lips of the sylvian fissure by more than 1 cm [Bodensteiner et al., in press; Tatum et al., 1989].

Seven patients had more than one neuroimaging study available for our review. None of the report studies demonstrated any detectable interval changes.

DISCUSSION

The fact that none of the patients with Sotos syndrome had normal MRI scans is not surprising; however, the fact that the abnormalities occur in such a characteristic pattern is an unexpected finding. Abnormalities of the corpus callosum, a nearly universal feature of Sotos syndrome, is associated with a striking incidence of other midline abnormalities. Although visual analysis of the relative size of the corpus callosum has been shown to be less reliable than quantitative analysis, we have not included quantitative analysis of the callosum in this context because despite the fact that the technology is available, most imaging centers do not have access to normal values for comparison [Bodensteiner et al., 1994].

Prominent trigones of the lateral ventricles, prominently enlarged occipital horns of the lateral ventricles, and the thinning of the posterior portion of the body of the corpus callosum may all be related to deficient or inadequate development of the posterior cerebral white matter. The cortical structures which would normally contribute axons to the posterior body of the corpus callosum cannot be assessed adequately with visual analysis of standard MRI scans. Nevertheless, the presence of these subjective structural abnormalities in patients with Sotos syndrome suggests that a search for corresponding functional deficits might provide confirmation of this characteristic abnormality. In fact, preliminary studies have shown a wide range of behavior problems and uneven patterns of scores on neuropsychological tests [Cole and Hughes, 1994].

The finding of two patients with an abnormally large cerebellum (macrocerebellum) is of interest. The presence of a macrocerebellum may be an indicator of disturbed cerebral development [Bodensteiner et al.,

TABLE I. Chief Neuroimaging Findings in 40 Patients With Classic Sotos Syndrome*

	Neuroimaging anomaly		Number
Ventricles	Large		25/40
	Prominent trigone		36/40
	Prominent occipital horn		30/40
Extracerebral fluid	Supratentorial		28/40
	Post. fossa		28/40
Midline anomalies	Cavum septum pellucidum		16/40
	Cavum vergae		15/40
	Cavum velum interpositum		7/40
	Macrocisterna magna		6/36
	Agenesis of CC		1/40
	Hypoplasia (thinning) of CC	Diffuse	12/36
		Particularly body	23/36
Migrational abn.	Heterotopias		3/36
Others	PVL		5/36
	Macrocerebellum		2/36
	Open operculum		1/40

* Abn., abnormality; Post., posterior; CC, corpus callosum; PVL, periventricular leukomalacia. Note: The denominator is 36 for some categories because the feature cannot be adequately defined by CT scan alone.

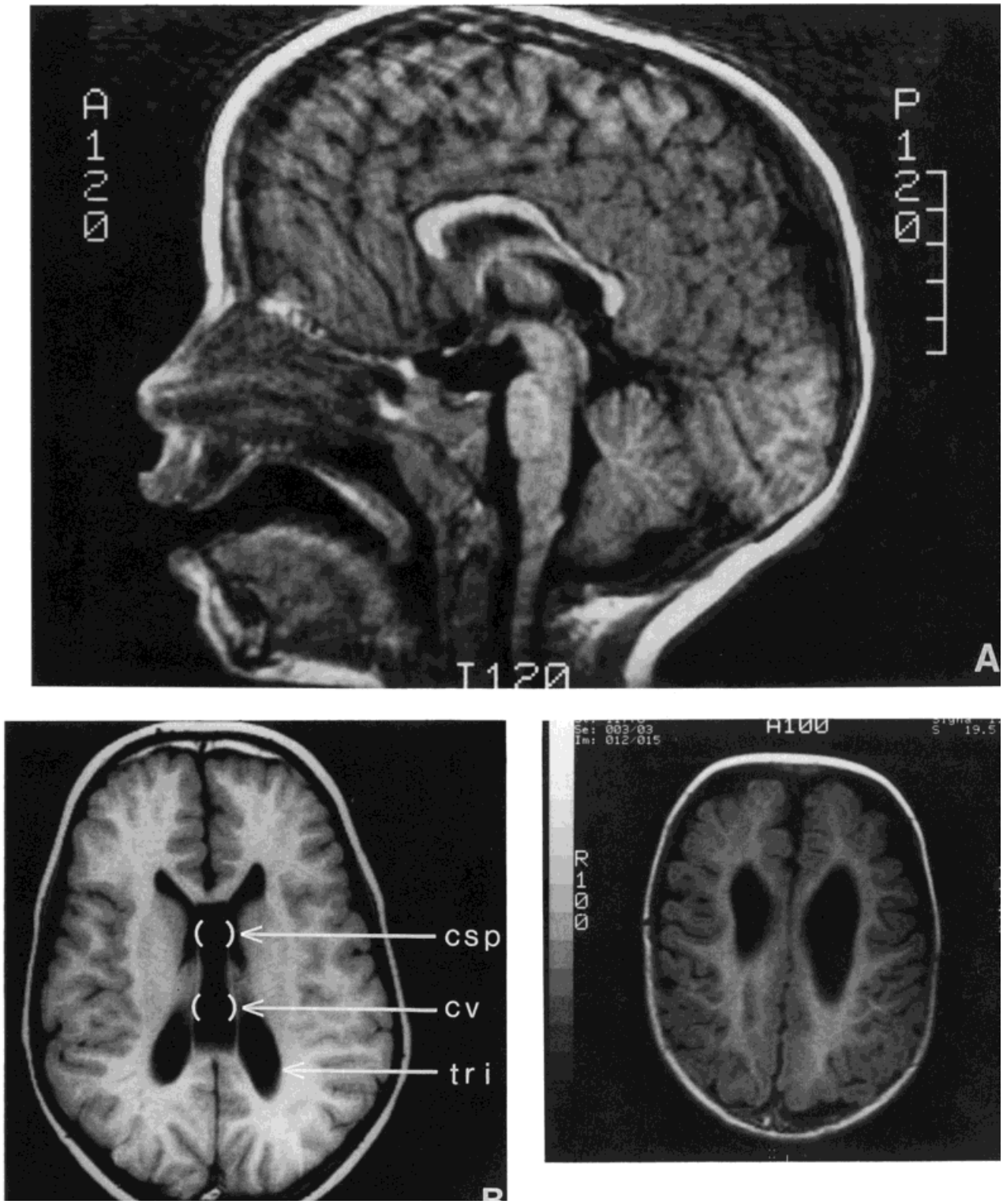

Fig. 1. **A:** T_1 weighted midsagittal MRI image of a patient with Sotos syndrome showing thinning of the posterior portion of the body of the corpus callosum with relative preservation of the genu, rostrum, and splenium. **B:** T_1 weighted axial MRI image shows a prominent trigone region of the lateral ventricles (tri). There is also a cavum septum pellucidi (csp) and cavum vergae (cv) in this patient. **C:** T_1 weighted axial MRI image of the brain showing prominent cerebral subarachnoid spaces characteristic of Sotos syndrome. The gyri are particularly prominent in the anterior half and in the interhemispheric fissure between the frontal lobes.

in press]. Three other anomalies, macrocisterna magna, open operculum, and heterotopias, also have implications with respect to the possibility of delayed or disturbed development of the brain. Gray matter heterotopias are a common and well-recognized indication of disturbed neuronal migration. The macrocisterna magna and the open operculum have recently been implicated as other manifestations of disturbed development or delayed maturation of the brain [Bodensteiner et al., 1988; Tatum et al., 1989].

Several of the other neuroimaging abnormalities of Sotos syndrome provide support for the hypothesis of delayed or disturbed development of the brain and particularly of midline structures. For example, it has been demonstrated that outside the neonatal period persistence of the cavum septum pellucidum, cavum vergae, and cavum velum interpositum are markers of disturbed midline brain development and associated with increased risk of mental retardation [Breeding et al., 1991; Miller et al., 1986].

A peculiarity of the behavioral patterns of patients with Sotos syndrome is that they tend to improve as they get older. One interpretation of this phenomenon is that these patients may have delayed maturation of the central nervous system which, to some extent, may improve as the child ages [Cole and Hughes, 1994]. The neuroimaging changes of Sotos syndrome appear to be at least compatible with the proposition that the brain development, particularly in the midline, is delayed and/or disturbed. This comment is not relevant to the one patient who had complete agenesis of the corpus callosum. The incidence of this finding in our study cohort (1/40, 3%) is the same as that reported in an unselected group of patients with mental retardation [Schaefer et al., 1991].

The enlarged CSF spaces and cerebral ventricles in these patients suggests that these children have normal size of brain inside a large head [Schaefer and Buehler, 1992]. However, most other syndromes with macrocephaly which we have encountered do not appear to share this combination of abundant ventricular and extracerebral fluid space [MacDonald and Schaefer, 1992; Olney et al., 1994; Schaefer et al., 1996]. We conclude that, in the proper clinical context, the neuroimaging findings in Sotos syndrome are distinctive. The pattern of abnormalities can aid in confirmation of the diagnosis and seems to suggest delayed or disturbed maturation of the brain in these individuals.

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